II. REMARKS

Formal Matters

Claims 1, 4-8, and 11-35 are pending after entry of the amendments set forth herein.

Claims 1, 4-8, and 11 were examined and were rejected. Claims 12-35 were withdrawn from consideration.

Claims 1 and 5 are amended. The amendments to the claims were made solely in the interest of expediting prosecution, and are not to be construed as an acquiescence to any objection or rejection of any claim. Support for the amendments to claims 1 and 5 is found in the claims as originally filed, and throughout the specification, in particular at the following exemplary locations: page 9, lines 9-12. Accordingly, no new matter is added by these amendments.

Please replace claims 1 and 5 with the clean version provided above.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE.**"

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Objection to specification

The Office Action stated that the upper margins of the specification are not large enough, and required a Substitute Specification with larger margins. A Substitute Specification is provided herewith.

As provided for under 37 C.F.R.§1.125, the undersigned Applicants' representative certifies that the Substitute Specification includes no new matter. A marked-up copy of the Substitute Specification is not provided, as the only objection to the specification as originally filed related to the margins.

Withdrawal of previous rejections

Applicants note with gratitude that the rejection of claims 1-11 under 35 U.S.C.§112, second paragraph, has been withdrawn.

Rejection under 35 U.S.C.§112, first paragraph

Claims 1, 4-8, and 11 were rejected under 35 U.S.C.§112, first paragraph, as allegedly lacking written description. Claims 1, 4-8, and 11 were rejected under 35 U.S.C.§112, first paragraph, as

allegedly lacking enablement.

Written description

The Office Action stated that the specification fails to set forth a disclosure of a specific agent; the specification fails to set forth exemplification that might demonstrate that the invention can be used successfully to reduce the plasma level of VLDL and triglycerides in a host; and the specification fails to set forth exemplification that might demonstrate that the invention can be used efficaciously to treat a host suffering from a disease condition associated with elevated levels of VLDL and/or triglycerides. The Office Action concluded that there is no factual evidence set forth in the specification that would reasonably convey to the skilled artisan that Applicants had possession of the claimed invention at the time the application was filed. Applicants respectfully traverse the rejection.

All that is necessary to fulfill the written description requirement is that one of skill in the art recognize that the Applicants invented what is claimed. MPEP §2163.02.

The Revised Interim Guidelines for Examination of Patent Applications Under 35 U.S.C. §112, paragraph 1 "Written Description" Requirement, (*Federal Register* (Dec. 21, 1999) Vol. 64 (No. 244):71427-71440) ("Revised Guidelines"), state:

(1) "There is a strong presumption that an adequate written description of the claimed invention is present when the application is filed";

(2) the Office has the initial burden of presenting evidence or reasons why a person skilled in the art would not recognize that the written description of the invention provides support for the claims;

(3) "Consequently, rejection of an original claim for lack of written description should be rare";

(4) an Examiner should review the entire application to understand what the applicant has described as the essential features of the invention; and

(5) the Examiner's review of the application is to be conducted *from a standpoint of one of skill in the art at the time the application was filed and should include a determination of the field of the invention and the level of skill and knowledge in the art* (emphasis added). Revised Guidelines, at page 71435.

The Office Action has not presented sufficient evidence or reasons why a person skilled in the art would not recognize that the written description of the claimed invention provides support for the claims.

As stated in the Revised Guidelines, "In most technologies which are mature, and *wherein the*

knowledge and level of skill in the art is high, **a written description question should not be raised for original claims even if the specification discloses only a method of making the invention and the function of the invention.**" Revised Guidelines, page 71436, emphasis added.

The present invention is based on the novel discovery that overexpression and accumulation of apoE causes hypertriglyceridemia by stimulating VLDL production and by impairing VLDL lipolysis. It necessarily follows that reducing the plasma level of active apoE will also reduce the plasma level of VLDL. Those skilled in the art are well aware of variety of agents that reduce expression of a coding region, including agents that affect promoter activity, antisense nucleic acids, and ribozymes.

The Office Action asserted that no factual evidence was presented to indicate that Applicants had successfully practiced at least a substantial number of the methods encompassed by the claims. However, fulfillment of the written description requirement of 35 U.S.C.§112, first paragraph, does not require that Applicants provide evidence of having successfully practiced the invention. To satisfy the written description requirement, Applicants need only reasonably convey to a person of ordinary skill in the relevant art that Applicants were in possession of the claimed subject matter. "In possession of" is not synonymous with "successfully practiced."

The Office Action asserted that the disclosure is limited to antisense oligonucleotides. However, the specification states that an agent suitable for use in the instant methods includes an agent that inhibits the expression of apoE. Specification, page 14, line 12. Those skilled in the art, as of the filing date, were well aware of various types of agents that inhibit expression of a coding region. There was no need to list each and every such agent. Nonetheless, the specification discusses exemplary classes of such agents: antisense nucleic acids, ribozyzmes, and antisense conjugates. Specification, page 14, line 12 to page 16, line 7; and page 16, lines 8-16.

The Office Action asserted that the description of antisense technology is so general that it would not reasonably convey to the skilled artisan that Applicants had possession of a method for reducing the plasma level of VLDL in a host be administering to the host an antisense molecule. The Office Action stated that the specification fails to describe the antisense oligonucleotides that can be used to successfully practice the method, or to describe regions of the polynucleotide sequence of the gene that can be effectively targeted by an antisense oligonucleotide so as to diminish expression of the gene.

However, as stated in the specification, the sequences of apoE mRNAs are known. Specification, page 15, lines 6-12. Because the nucleotide sequences of apoE mRNAs are known, the sequences of antisense are also known, and need not be provided in the specification. Applicants note that it is well established that a "patent need not teach, and preferably omits, what is well known in the art." MPEP §2164.01.

As of the priority date of the instant application, several texts were published, which provided detailed descriptions of how to make and use antisense nucleic acids. See, e.g., "Antisense and Ribozyme Methodology: Laboratory Companion" I. Gibson, ed., Chapman & Hall (1997); and "Applied Antisense Oligonucleotide Technology" C.A. Stein and A.M. Krieg, eds., Wiley-Liss (1998). These texts are evidence for the fact that those skilled in the art as of the priority date knew that all one needs to make antisense nucleic acids is to know the sequence of at least part of the gene being targeted. The fact that the entire sequence of the apoE gene was available to Applicants would make it clear to those skilled in the art that Applicants had possession of a method involving reducing expression of apoE.

The Office Action stated that the disclosure fails to describe the level of inhibition of expression of the gene that might be achieved in practicing the claimed method, or which level of inhibition must be attained to effectively reduce the plasma level of VLDL in the host. However, the Examples describe the level of apoE3 expression that results in elevated levels of VLDL production in experimental animals in two different mammalian systems.

Transgenic mice expressing low levels of human apoE3 (e.g., about 13 mg/dl) exhibited substantially normal levels of VLDL, while transgenic mice expressing high levels of apoE (e.g., about 30 mg/dl or higher) exhibited elevated levels of VLDL. Specification, page 30, lines 18-28; and page 31, lines 12-13. Transgenic rabbits expressing low levels of human apoE3 (e.g., about 6.5 mg/dl or 15 mg/dl) exhibited substantially normal levels of VLDL, while transgenic rabbits expressing high levels of apoE3 (e.g., more than about 20 mg/dl) exhibited elevated levels of VLDL. Specification, page 37, line 24 to page 38, line 2.

The Office Action stated that the disclosure must include a description of at least a substantial or at least a representative number of embodiments of the methods encompassed by the claims, and of

sufficient detail to satisfy a factual inquiry to determine whether the skilled artisan would have reasonable cause, given only the benefit of Applicants' original disclosure, to accept the assertion that Applicants had possession of the claimed invention as of the filing date. However, as discussed above, those skilled in the art would recognize that Applicants had possession of the claimed invention, given: (1) the ample evidence of levels of apoE3 expression that lead to elevated VLDL levels; (2) the fact that the sequence of the apoE3 gene was known and available to Applicants; (3) the high level of skill of those in the field of controlling gene expression; and (4) the ample information in the art regarding how to modulate expression of genes whose sequences are known.

Enablement

The Office Action stated that the teachings of the specification cannot be extrapolated to the enablement of the invention because the amount of guidance, direction, and exemplification disclosed in the specification is not reasonably commensurate in scope with the claims.

The law regarding enablement of inventions is clear: "[t]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation."[1]

To aid in determinations of enablement, courts have identified eight factors for consideration: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability or unpredictability of the art; and (h) the breadth of the claims.[2]

> The specification provides ample guidance such that one skilled in the art could use the specification, coupled with that which is known in the art, to practice the claimed invention. Applicants describe several methods of decreasing expression of apoE on page 14, line 12 through page 16, line 16. Once a skilled artisan has identified a gene target, reducing its expression is well within that artisan's skill. For example, since the nucleotide sequence of apoE is known, one of skill in the art would fully expect to be able to use antisense technology to reduce apoE expression. Furthermore, researchers, such as Charpentier et al. ((2000) *Biochemistry* 39:16084-91, a copy of which was provided along with the response to the Office

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[1] *United States v. Telectronics, Inc.*, 8 USPQ 2d 1217, 1233 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989). See also *Genentech, Inc. v. Novo Nordisk*, 42 USPQ 2d 1001 (Fed. Cir. 1997), *cert. denied*, 522 U.S. 963 (1997); *Scripps Clinic and Research Foundation v. Genentech, Inc.*, 18 USPQ 2d 1001 (Fed. Cir. 1991).

[2] *Ex Parte Forman.*, 230 USPQ 546, 547 (Bd.Pat.App & Interf. 1986); and, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Action mailed August 9, 2001) have already demonstrated that antisense technology can be used to reduce apoE expression.

Applicants respectfully submit that the specification and the claims, coupled with the information known in the art, would enable one of skill in the art to use the invention without undue experimentation. Relevant enablement factors are discussed in detail below.

(a) the quantity of experimentation necessary:

The courts have clearly taught that the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. For example, see MPEP §2164.01.[3]

As the court explained[4]:

> "[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed."

Practitioners in the chemical and molecular biology arts frequently engage in extensive modification of reaction conditions and complex and lengthy experimentation where many factors must be varied to succeed in performing an experiment or in producing a desired result. The Federal Circuit has found that such extensive experimentation is not undue in the molecular biology arts. For example, the court concluded that extensive screening experiments, while being voluminous, were not undue in view of the art which routinely performs such long experiments.[5]

The claims recite methods involving reducing the amount of plasma active apoE in a host by reducing the expression of apoE in the host. The only experiments, if any, that need be performed to enable the entire scope of the claim are those designed to determine which factors, such as antisense, small molecules that affect expression, ribozymes, and the like, that reduce expression of apoE. As an example, the sequence of an antisense nucleic acid that reduces apoE expression is determined through routine experimentation that is empirical in nature, typically employing nothing more than performing the same assay disclosed in the specification on a variety of antisense nucleic acids made by routine recombinant DNA techniques. For example, a suitable assay for determining the effect of apoE expression levels on VLDL triglyceride production *in vitro* is described in the specification on page 29, line 21 to page 30, line 7. In this assay, rat hepatoma cells transfected *in vitro* with an apoE-encoding construct were assayed for VLDL production, and the effect of the level of apoE expression on VLDL production was studied. Since these experiments are empirical in nature, no undue experimentation is required. In other

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[3] See also *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 227 USPQ 428 (Fed. Cir. 1985).
[4] *In re Wands* 8 USPQ 2d at 1404
[5] *Hybritech v. Monoclonal Antibodies, Inc.* 231 USPQ 81 (Fed. Cir. 1986)

words, the only experimentation that may be required to enable the claimed invention are those experiments to determine the level of VLDL production, and since this only requires a routine assay on various antisense nucleic acids to determine the effects of same on VLDL production, no undue experimentation is necessary.

(c) the presence or absence of working examples:

Compliance with the enablement requirement under Section 35 U.S.C. §112, first paragraph does not require or mandate that a specific example be disclosed. The specification need not contain a working example if the invention is otherwise disclosed in such a manner that one skilled in the art would be able to practice the invention without undue experimentation.[6] Furthermore, "Nothing more than objective enablement is required, and therefore it is irrelevant whether [a] teaching is provided through broad terminology or illustrative examples."[7]

(f) the relative skill of those in the art:

The relevant ordinarily skilled artisan is generally a skilled laboratory technician with experience in molecular biology and/or a scientist with the equivalent of a doctoral degree in molecular biology techniques. Furthermore, such artisans are required to keep abreast of the latest technology through continuing education and reading of scientific journal articles. As such, the skill level of those developing and using methods for manipulating DNA and performing cell-based assays is high.

Furthermore, as discussed above, several texts exist (in addition to abundant literature in scientific journals), which provide ample description of how to make and use antisense nucleic acids. Still further, those skilled in the art are well aware of how to modulate expression of a gene, once the sequence of the gene is known.

A search of the PubMed database (available via the National Center for Biotechnology Information web server) for the word "antisense" in the title of an article resulted in 4178 articles about uses of antisense technology (the first 25 pages of the search results are attached as Exhibit A). For example, Sze et al. (Neurochem. Int. (2001) 39:319-327 (copy enclosed)) reports the successful use of antisense to block both the mRNA and protein expression of NR2B in neurons and Finegold et al. (Mol. Brain Res. (2001) 90:17-25 (copy enclosed)) reports the development of an antisense gene therapy to

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[6] In re Borkowski, 164 USPQ at 645.
[7] *In re Robins* 166 USPQ 552 at 555 (CCPA 1970).

modulate the NMDA type of glutamate receptor. Furthermore, as noted above Charpentier et al. demonstrates the use of antisense technology to reduce expression of apoE.

Antisense technology has also reached the point where numerous antisense oligonucleotides are in clinical trials. For example, Tamm et al. (Lancet (2001) 358:489-497 (copy enclosed)) provides an overview of antisense therapy and provides a list of antisense oligonucleotides that are either in clinical trials or are already approved for use (see page 490). Agrawal and Kandimalla (Mol. Med. Today (2000) 6:72-81 (copy provided along with response to August 9, 2001 Office Action)) list 16 antisense oligonucleotides that are being investigated for clinical use in treating oncological, hematological and viral diseases (see page 74). The article concludes with the following statement:

> Many questions about the effects of **antisense oligonucleotide** sequence, secondary structures, cellular uptake, metabolism, excretion, tissue distribution, side effects and mechanism of action have been answered to a large extent, if not completely, in the past few years.

Page 80 (emphasis in original). Thus, contrary to the assertions contained in the Office Action, the use of antisense technology to reduce gene expression is well within the ability of one skilled in the art and would require no more than routine experimentation.

(g) the predictability or unpredictability of the art

In making this rejection, the Office Action asserts that the antisense art is unpredictable, and two references are provided in support of this argument. The Office Action asserts that because the art is unpredictable, the specification is not enabling.

The Office Action cited various references to support the contention that antisense technology is unpredictable. However, the Office Action merely presents isolated references discussing problems associated with the technology. There are problems associated with every technology. Antisense technology is no exception. The possibility that there may be problems does not lead to a conclusion that the instant specification lacks enablement. Furthermore, the overwhelming consensus in the field -- as evidenced by the above-cited texts, other texts not cited herein, as well as the thousands of literature references describing successful application of antisense technology, the fact that numerous clinical trials are underway which employ antisense technology -- is that antisense technology works, and that those in the field, given the sequence of a gene, can make and use antisense nucleic acids.

The Office Action cited Sohail et al. ((2000) *Curr. Opinions Mol. Ther.* 2:264:271; "Sohail"); and Pierce et al. ((1998) *Nucl. Acids Res.* 26:5093-5101; "Pierce") to support the assertion that antisense technology is unpredictable. Sohail states that predicting the optimal sequence of an antisense nucleic acid that will bind to a

given sense nucleic acid is difficult. However, Sohail states that empirical approaches to identifying an antisense nucleic acid that hybridizes with a given sense nucleic acid are successful. Thus, one cannot conclude from reading Sohail that antisense technology as a whole is unpredictable, since empirical determination of antisense sequences results in success. At most one can conclude that some experimentation is involved to identify an antisense nucleic acid that will hybridize with a given sense nucleic acid. As discussed above, a substantial amount of experimentation is allowed, if it is routine; and such experimentation would in fact be routine. As with Sohail, Pierce merely discusses predicting the optimal sequence of a ribozyme nucleic acid. Pierce discusses a method for identifying ribozymes that are effective in modulating gene expression. Thus, one cannot conclude from Pierce that antisense is unpredictable, since Pierce discusses methods for identifying functional ribozymes.

Indeed, the findings of Charpentier et al., which demonstrated that antisense technology can be used to reduce apoE expression, appear to contradict the assertion that antisense technology is unpredictable.

The Office Action stated that delivery of antisense agents has wrought undesirable, adverse, non-specific toxicity. However, issues of toxicity and unwanted side effects are outside of the purview of the U.S. Patent and Trademark Office. Instead, such issues are addressed by the FDA. See MPEP §2107.02, section V. As stated in the MPEP (§2107.02, section V), it is improper for Office personnel to request evidence of safety in the treatment of humans.

The Office Action stated that Lesoon-Wood et al. ((1999) *Cancer Letters* 147:163-173; "Lesoon-Wood") discovered that control antisense molecules caused a considerable level of non-specific inhibition. However, such activity on the part of control antisense nucleic acids is the exception, rather than the rule. An isolated reference discussing problems that researchers may have had with particular antisense does not lead to a conclusion that the instant invention as claimed is not enabled. Furthermore, the instant claims require that the agent reduce apoE levels to a degree sufficient to reduce VLDL production. Agents that do not have such activity are not within the scope of the claim.

The Office Action asserted that there is evidence that reducing the level of apoE expression in a host may not be an effective means for treating a patient diagnosed with a disease associated with dyslipidemia. In support of this statement, the Office Action cited Ishigami et al. ((1998) *J. Biol. Chem.* 273:20156-20161; "Ishigami"); and Huang et al. Ishigami discusses protective effects of apoE through inhibition of cell signaling events associated with growth factor-induced smooth muscle cell migration and proliferation. However, a reduction in apoE expression to an extent sufficient to reduce VLDL does not preclude a protective effect of apoE against vascular disease. The Office Action has not produced any reasoning why a reduction in apoE expression to an

extent sufficient to reduce VLDL would preclude a protective effect of apoE against vascular disease. The Office Action has not substantiated the assertion that "reducing the level of apoE expression in a host may not be an effective means for treating a patient diagnosed with a disease associated with dyslipidemia."

The Office Action stated that the courts have determined that antisense technology is highly unpredictable, citing *Enzo Biochem. Inc., v. Calgene, Inc.* 52 USPQ2d 1129 (CAFC, 1999); "*Enzo.*" However, *Enzo* does not support a conclusion that the instant claims are not enabled. As noted in *Enzo*, whether claims are sufficiently enabled by a disclosure in a specification is determined as of the date that the patent application was first filed. The patents in question in *Enzo* had an effective filing date of October 20, 1983. As stated in *Enzo*, "an enablement determination is made retrospectively, i.e., by looking back to the filing date of the patent application and determining whether undue experimentation would have been required to make and use the claimed invention at that time. *Enzo* at 1134. A finding of lack of enablement of a patent having an effective filing date of October 20, 1983 cannot be applied to the instant patent application having an effective filing date of March 12, 1999, because the field has advanced profoundly in the intervening 16 years.

Furthermore, *Enzo* is a review of patent claims that "attempt to include the entire universe of cells for the antisense system detailed." *Enzo*, at 1134. The instant claims are not directed to "a prokaryotic or eukaryotic cell containing a non-native DNA construct, which construct produces an RNA which regulates the function of a gene," as did the patents under review in *Enzo*. Instead, the instant claims recite use of an agent that reduces expression of a apoE, for which the sequence was known as of the effective filing date.

Furthermore, the courts have clearly taught that even in unpredictable arts the specification does not have to disclose every species of a genus that would work and every species that would not work.

The court has very clearly explained[8]:

> "To require such a complete disclosure would apparently necessitate a patent application or applications with thousands of catalysts....More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed. A potential infringer could readily avoid literal infringement of such claims by merely finding another analogous catalyst complex which could be used ...."

(h) the breadth of the claims

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[8] *In re Angstadt*, 190 USPQ at 218.

The claims of the instant application only require that the level of apoE expression be reduced by an amount sufficient to reduce VLDL production. *Thus, the claim language excludes agents that do not reduce apoE expression to such an amount.*

In sum, the amount of experimentation required to practice the claimed methods would not be undue because a) the sequence of an apoE gene is known; b) guidance is given on how to test whether a give agent reduces apoE to a level sufficient to reduce VLDL production; c) there is ample guidance in the art for how to make and use agents, such as antisense nucleic acids, that reduce apoE expression; and d) one of skill in the art would be able to perform, as a matter of routine, experiments to determine whether a given agent reduces apoE expression to the requisite degree.

The specification therefore provides sufficient enablement such that one of ordinary skill in the art would be able to practice the invention without undue experimentation.

Conclusion

Applicants submit that the rejection of claims 1, 4-8, and 11 under 35 U.S.C. §112, first paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejection under 35 U.S.C.§102(b)

Claims 1, 4-8, and 11 were rejected under 35 U.S.C.§102(b) as allegedly anticipated by Ditschuneit et al. . ((1992) *J. Int'l. Med. Res.* 20:197-210; "Ditschuneit") as evidenced by Pedreno et al. and Durrington et al. Claims 1, 3-8, 10, and 11 were rejected under 35 U.S.C.§102(b) as allegedly anticipated by Yoshino et al. ((1989) *Atherosclerosis* 75:67-72; "Yoshino"). Claims 1, 3-8, 10, and 11 were rejected under 35 U.S.C.§102(b) as allegedly anticipated by Connor et al ((1993) *Ann. N.Y. Acad. Sci.* 683:16-34; "Connor"). Claims 1, 5, 6, and 11 were rejected under 35 U.S.C.§102(b) as allegedly anticipated by Kasiskie et al. ((1990) *Am. J. Kidney Dis.* 15:8-15; hereinafter "Kasiskie") as evidenced by Wyne et al. ((1989) *J. Biol. Chem.* 264:16530-16536; hereinafter "Wyne").

Claims 1, 4-8, and 11; Ditschuneit

The Office Action asserted that Ditschuneit et al. teaches a method of treating female patients with hyperlipoproteinaemia type IV with gemfibrozil and that the mechanism by which an agent acts to treat a disease is an inherent property of that agent. The Office Action then pointed to Pedreno et al. and Durrington et al., asserting that they teach that gemfibrozil causes a reduction in levels of triglyceride, VLDL and apoE in a patient. The Office Action asserted that all the limitations of the claims are anticipated by the teachings of Ditschuneit. Applicants respectfully traverse the rejection.

Gemfibrozil increases LDL receptor expression. The instant claims recite use of an agent that reduces expression of apoE. Gemfibrozil does not reduce expression of ApoE. Nothing in the cited references teaches that gemfibrozil reduces expression of apoE. Thus, the claimed invention and the mechanism of gemfibrozil are not the same. Accordingly, Ditschuneit et al., as evidenced by Pedreno et al. and Durrington et al., does not anticipate claims 1, 4-8, and 11.

The Office Action asserted that the claims are not limited to a method in which the level of transcription of the gene encoding apoE is reduced, or in which the level of translation of mRNA encoding apoE is reduced. However, the claims recite administering an agent that acts by "reducing the expression of apoE." "Reducing the expression of apoE" is an art term understood by those in the field to refer to reducing transcription of the gene encoding apoE and/or translation of an mRNA encoding apoE.

The Office Action stated that "it is reasonable to expect that gemfibrozil affects the expression of apoE." However, this is an assertion without basis in fact. The Office Action has presented no evidence whatsoever that gemfibrozil affects the expression of apoE. The Office Action stated that gemfibrozil is deemed the same as the agent of the present claims. The initial burden is on the Office to provide reasoning or facts to substantiate the assertion that gemfibrozil affects expression of apoE. MPEP §2112. The Office Action has not provided such reasoning or facts.

The Office Action stated that Clavey et al. ((1999) *Cell. Physiol. Biochem.* 9:139-149; "Clavey") reported that fibrates repress apolipoprotein CIII gene expression. The Office Action concluded that the mechanism of gemfibrozil is not limited to increasing LDL receptor expression. However, Clavey does not disclose any effect of gemfibrozil on apoE expression. The Office Action has provided no basis for extrapolating an effect on apolipoprotein CIII gene expression to an effect on expression of any other

gene.

Claims 1, 3-8, 10, and 11; Yoshino

Applicants note for the record that claims 3 and 10 are not currently pending in this application. Accordingly, the rejection will be addressed as it might be applied to claims 1, 4-8, and 11.

The Office Action stated that Yoshino teaches a methods for treating patients diagnosed with a disease associated with elevated plasma levels of VLDL and triglycerides, by administering pravastatin to reduce the concentrations of apoE, VLDL, and triglycerides. The Office Action asserted that Yoshino anticipates claims 1, 4-8, and 11. Applicants respectfully traverse the rejection.

There is no evidence that pravastatin acts to decrease plasma VLDL level by reducing expression of apoE. There is evidence that it acts through a different mechanism in that it is a competitive inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This inhibition of HMG-CoA reductase leads to upregulation of the LDL receptor, which, in turn, leads to enhanced clearance of plasma VLDL. Since apoE is a component of the VLDL particles, apoE levels will also be reduced when VLDL is cleared; however, this decrease in apoE is not the result of decreased expression as the claims require. Nothing in the references teach that pravastatin reduces expression of apoE or that reducing apoE expression will reduce VLDL production and consequently reduce the plasma VLDL level.

The Office Action acknowledged that pravastatin is known to be an inhibitor of HMG-CoA reductase. The Office Action stated that Applicants have not provided evidence that pravastatin does not affect the level of plasma VLDL by some other mechanism, such as directly affecting the level of expression of apoE. However, the initial burden is on the Office to provide reasoning or facts to substantiate the assertion that pravastatin affects expression of apoE. MPEP §2112. The Office Action has not provided such reasoning or facts. Indeed, such an assertion appears to be at odds with the Office Action's acknowledgement that pravastatin is an HMG-CoA reductase inhibitor.

The Office Action stated that Wyne et al. ((1989) *J. Biol. Chem.* 264:16530-16536; "Wyne") teaches that mevinolin, an inhibitor of HMG-CoA reductase, attenuates stimulation of transcription of

the gene encoding apoE in rat granulosa cells upon exposure to cholera toxin or TPA. However, Wyne does not discuss pravastatin. Furthermore, Wyne states that HMG-CoA reductase is a rate-limiting enzyme in cholesterol synthesis and as such reduces the level of downstream products. Wyne does not disclose that mevinolin, or any other inhibitor of HMG-CoA reductase, reduces apoE expression.

Thus, there is nothing in Yoshino to suggest that pravastatin decreases plasma VLDL levels by reducing apoE expression. Accordingly, Yoshino cannot anticipate claims 1, 4-8, and 11.

Claims 1, 3-8, 10, and 11; Connor

Applicants note for the record that claims 3 and 10 are not currently pending in this application. Accordingly, the rejection will be addressed as it might be applied to claims 1, 4-8, and 11.

The Office Action stated that Connor teaches a method for treating patients diagnosed with a disease associated with elevated plasma levels of VLDL and triglycerides by administering an effective amount of dietary n-3 fatty acids. The Office Action concluded that all of the limitations of the claims are anticipated by Connor. Applicants respectfully traverse.

Connor does not disclose that apoE is a target for reducing the plasma level of VLDL or that reduction of apoE expression will cause a reduction in VLDL production and thereby also reduce plasma VLDL, while there is evidence that n-3 fatty acids act through a different mechanism. As noted previously, if the cited agent decreased VLDL production by decreasing apoE, one of skill in the art would expect that it would have other effects opposite to that of an overexpression of apoE. Huang et al. (cited in previous Response) teaches that increased apoE results in normal or decreased LDL levels by impairing VLDL lipolysis; however, Connor et al. states that dietary n-3 fatty acids caused a reduction in LDL. This is the opposite effect on LDL level that would be expected if n-3 fatty acids acted by decreasing apoE expression and would lead one of skill in the art to believe that the mechanism of action is not through apoE expression. Connor et al. further states that dietary n-3 fatty acids reduce synthesis of triglyceride and VLDL in the liver and shorten turnover of VLDL in the plasma. This statement is supported by both Harris ((1989) *J. Lipid Res.* 30:785-807 (abstract provided along with the response to the August 9, 2001 Office Action)) and Hebbachi et al. ((1997) *Biochem. J.* 325:711-9 (abstract provided along with the response to the August 9, 2001 Office Action)). Furthermore, Anil et al. ((1997) *Biochem. Mol. Biol. Int.* 43:1071-80 (abstract provided along with the response to the August

9, 2001 Office Action)) report that the effect of n-3 fatty acids on hepatic VLDL production is mediated through prostaglandins. Nothing in the references teach that dietary n-3 fatty acids reduce expression of apoE or that reducing apoE expression will reduce VLDL production and consequently reduce the plasma VLDL level.

Thus, there is nothing in Connor *et al.* to suggest that dietary n-3 fatty acids decrease VLDL production by reducing apoE expression. Accordingly, Connor cannot anticipate claims 1, 4-8, and 11.

Claims 1, 5, 6, and 11; Kasiskie

The Office Action stated that Kasiskie teaches a method for treating patients diagnosed with a hyperlipidemia, involving administering an effective amount of lovastatin, an inhibitor of HMG-CoA reductase.

The Office Action acknowledged that lovastatin is an inhibitor of HMG-CoA reductase. There is no evidence in Kasiskie that lovastatin acts to decrease plasma VLDL levels by reducing expression of apoE.

The Office Action stated that, as evidenced by the teachings of Wyne, mevinolin (lovastatin) attenuates production of mRNA encoding apoE in cells. However, as discussed above, Wyne states that HMG-CoA reductase is a rate-limiting enzyme in cholesterol synthesis and as such reduces the level of downstream products. Wyne does not disclose that mevinolin reduces apoE expression.

Conclusion

Applicants submit that the rejection of claims 1, 4-8, and 11 under 35 U.S.C. §102(b has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Objection to claim 3

The Office Action sated that claim 3 is objected to as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicants note that claim 3 is not currently pending, having been canceled without prejudice to renewal in the amendment, responsive to the August 9, 2001 Office Action and filed November 8, 2001. Accordingly, any objection to claim 3 is moot.

Rejection under 35 U.S.C.§112, second paragraph

Claims 1, 4-8, and 11 were rejected under 35 U.S.C.§112, second paragraph, as allegedly indefinite.

The Office Action stated that claims 1, 4-8, and 11 are vague and indefinite because claims 1 and 5 recite the term "reducing" or "reduce." The Office Action asserted that these terms are relative terms. The Office Action further asserted that the specification provides no standard for ascertaining the requisite degree to which the levels of plasma actiave apoE, apoE expression , VLDL expression, and plasma VLDL must be reduced. Applicants respectfully traverse the rejection.

The terms "reducing" and "reduce" are not relative terms. MPEP §2173.05(b). The claims recite that the plasma level of VLDL is reduced. Thus, any reduction of apoE expression that is sufficient to achieve a reduction in plasma levels of VLDL is encompassed by the instant claims. Thus, the claims are not indefinite and need not be amended.

Nevertheless, and solely in the interest of expediting prosecution, claims 1 and 5 are amended to recite that plasma level of VLDL (claim 1) and VLDL production (claim 5) are reduced by at least about 2 fold.

The Office action stated that claims 1, 4-8, and 11 are vague and indefinite in reciting "at least reduces." Without conceding as to the correctness of the rejection, claims 1 and 5 are amended to delete "at least."

The Office Action stated that claim 2 is indefinite. Applicants note that claim 2 is not currently pending in this case. Therefore, the rejection of claim 2 is moot.

The Office Action stated that claims 5-8 and 11 are indefinite because claim 5 recites "to treat said disease condition." The Office Action stated that recitation of the phrase renders the claim indefinite because it is unclear to what effect the disease condition is treated.

The meaning of this rejection is not entirely clear. Claim 5 as amended recites that VLDL production is reduced by at least about 2 fold. Disease conditions associated with elevated levels of VLDL are thus treated when VLDL production is reduced. The specification provides a description of "treatment." Specification, page 19, line 26 to page 20, line 6. Thus, the term is not indefinite, and the

claim need not be amended.

The Office Action stated that claims 5 and 11 are vague and indefinite because claim 5 recites "a disease condition associated with elevated plasma levels of VLDL." The specification provides a discussion of disorders associated with elevated plasma levels of VLDL. Specification, page 19, lines 12-25. Disorders associated with elevated plasma levels of VLDL are known in the art. Accordingly, claims 5 and 11 are not indefinite and need not be amended.

Nevertheless, and solely in the interest of expediting prosecution, claim is amended to recite that the disease condition being treated is a hyperlipidemia.

Applicants submit that the rejection of claims 1, 4-8, and 11 under 35 U.S.C. §112, second paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number UCAL121.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: Sept. 16, 2002

By: _____
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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Please enter the amendments to claims 1 and 5, as shown below.

1. (Three Times Amended) A method for reducing the plasma level of VLDL in a host, said method comprising:

administering to said host an effective amount of an agent which [at least] reduces the amount of plasma active apoE in said host by reducing the expression of apoE by an amount sufficient to reduce VLDL production in said host to reduce the plasma level of VLDL in said host, whereby the plasma level of VLDL in said host is reduced by at least two fold.

5. (Three Times Amended) A method of treating a host suffering from a disease condition associated with elevated plasma levels of VLDL, said method comprising:

administering to said host an effective amount of an agent that [at least] reduces the plasma amount of active apoE in said host by reducing the expression of apoE by an amount sufficient to reduce VLDL production by at least two fold to treat said disease condition, whereby said host is treated.